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Assistant Commissioner for Patents
U.S. Dept. of Commerce / Patent & Trademark Office
Attn: Examiner Dwayne C. Jones, AU 1614
Washington, D.C. 20231

Sent via Fax & Express Mail **OFFICIAL**

RE: Pat. Application #09/781,491
Clouatre, et al., Methods And Pharmaceutical Preparations For Normalizing Blood Pressure With (–)-Hydroxycitric Acid
Office Action of 06/06/2003 in response Inventor's document mailed 01/20/03

Dear Examiner Jones:

In reviewing the most recent Office Action, what stands out is that the interpretation of US Patent #6,221,901 by Shrivastava, et al. turns upon the nature of the substance — magnesium (–)-hydroxycitrate — for which the claims of that patent are being made. Shrivastava, et al. do indeed make a claim regarding hypertension, but for what? The Office Action never addresses the issue of the definition of the substance to which the teachings of Shrivastava, et al. inhere, but rather assumes what is in need of judgment. This is done despite the fact that in both of the previous responses by Clouatre, et al. it was pointed out that the interpretation put forth by the Office Action is systematically at odds with the wording and examples found in Shrivastava, et al. Furthermore, if the interpretation found in the Office Action is allowed, Shrivastava, et al. clearly and obviously must be faulted for having failed to list prior art. This indicates on its face that the interpretation upon which the Office Action is based cannot be the proper one.

Moreover, the present Office Action presents a number of assertions regarding what "one skilled in the art" would have known with regard to magnesium (–)-hydroxycitrate according to the teaching of Shrivastava, et al., assertions that fail, first, because of the incorrect and unexamined initial assumption regarding the nature of the compound; second, because of a number of unjustified leaps in logic that lead to obvious falsehoods when applied to any number of other known compounds; and, third, because one or more of the assertions are empirically false.

Clouatre, et al., also object to the characterization of our previous response as presented in the current Office Action, ¶ 3 and 4 and the justification given for the Office Action's not addressing a key argument. The patent by Lowenstein and other prior art were discussed by us because this prior art bears directly on the interpretation of the nature of the claims being made by Shrivastava, et al., in particular, the nature of the compound. Again, the interpretation offered in the various Office Actions leads directly to infringements on prior art and therefore cannot possibly be an acceptable interpretation unless one deems the patent by Shrivastava, et al. itself to have been issued in error. Hence, Clouatre, et al. offer a different determination of the substance to which the claims of Shrivastava, et al. can be applied without introducing confusions vis-a-vis previous patent claims and other prior art. Despite the assertion in the Office Action in

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¶ 4, Clouatre, et al. quite directly respond to paragraphs 4 and 5 of the the Office Action dated 25 November 2002 in our letter of 20 January 2003. Contrary to the characterization found in the present Office Action, we note here that *it is this and the previous Office Actions that have not addressed issues.*

As for the comment that we argued that Shrivastava, et al. did not test the anti-hypertensive properties of magnesium (–)-hydroxycitrate, this certainly is true — the example given is not such a test. We pointed out that inasmuch as the patent's test used an obviously toxic dose of magnesium, the claimed hypotensive effect is actually the result of osmotic diarrhea from the magnesium and not a demonstration of the hypotensive effect of magnesium (–)-hydroxycitrate.

However, the further point of our observation was and is that since the mineral magnesium in its various forms has been known for decades to have hypotensive benefits when given at physiologic dosage levels, the experiment described by Shrivastava, et al. does not prove anything. Was it the magnesium that was active, the (–)-hydroxycitric acid, or the former only with the latter as a ligand? The experiment as described by Shrivastava, et al. does not *and cannot* tell us anything new with regard to hypertension.

Outside of the hypertension example, Shrivastava, et al. everywhere else pointedly contrast their results found with magnesium (–)-hydroxycitrate with those found with (–)-hydroxycitric acid and with magnesium and explicitly claim that theirs is a "new compound" different from other items based on (–)-hydroxycitric acid (column 2, lines 9-12). So what is this "new compound?" The answer to this question directly determines the nature and scope of the claims allowable to Shrivastava, et al.

There would appear to be only a limited number of possible choices with regard to the subject matter of Shrivastava, et al., to wit:

a) magnesium (–)-hydroxycitrate is an entirely new substance
b) magnesium (–)-hydroxycitrate is a special salt of magnesium *unique due to its ligand (–)-hydroxycitric acid*, which gives this form of magnesium special properties
c) magnesium (–)-hydroxycitrate is a form of (–)-hydroxycitric acid identified by the choice of the alkaline earth metal magnesium used to produce the salt with properties shared by all other forms of the acid and its salts
d) magnesium (–)-hydroxycitrate is a new compound of (–)-hydroxycitrate with properties that are unique to itself and not shared with (–)-hydroxycitric acid or other salts of (–)-hydroxycitric acid

The Office Action simply assumes that (c) is the correct choice. It then proceeds to argue — wrongly — that 1) Shrivastava, et al. establish the interchangeability between (–)-hydroxycitrate and (–)-hydroxycitric acid; and 2) what has been established for magnesium (–)-hydroxycitrate would be extended by "one skilled in the art" to other forms of (–)-hydroxycitric acid. However, the position championed in the Office Action:

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a) contradicts directly the characterization by Shrivastava, et al. of their own patent
b) introduces internal inconsistencies into Shrivastava, et al.
c) maintains what is never demonstrated in the Action nor in the patent
d) makes problematic the interpretation of prior art, including prior patents

These issues are dealt with under separate sections below as follows:

I Shrivastava, et al. claim magnesium (–)-hydroxycitrate is a "new compound" and deny the interchangeability between (–)-hydroxycitrate and (–)-hydroxycitric acid

II Arguments from old chemistry text in Office Action wrongly extend remarks regarding carboxylic acids to tricarboxylic acids; errors both in logic and in fact, confusions in the Office Action as to whether it is the cation or the ligand that is active, etc.

III Office Action remarks ¶14 based on DiPiro, et al. are partially contradicted even by the text being cited, improperly extend *inter alia* arguments and have no clear bearing on Clouatre, et al.

IV Proper characterization of Shrivastava, et al. to avoid conflicts with prior art and/or the conclusion that Shrivastava, et al. was issued in error

V Claims made for magnesium with (–)-hydroxycitric acid as a ligand (Shrivastava, et al.) versus claims made for (–)-hydroxycitric acid with or without magnesium as a cation (Clouatre, et al.)

I Shrivastava, et al. claim magnesium (–)-hydroxycitrate is a "new compound" and deny the interchangeability between (–)-hydroxycitrate and (–)-hydroxycitric acid

In the present Office Action, ¶ 4 at the top of page 3 and referring to the previous Office Action of 25 November 2002, it is stated that one skilled in the art, especially after using the teachings of Shrivastava, et al., would look to substitute or replace one pharmaceutically acceptable cation for another, such as sodium or potassium or calcium. Later (apparently citing to column 2, lines 34-48, although this material is not found there), the present Office Action further maintains that Shrivastava, et al. establish the interchangeability between (–)-hydroxycitrate and (–)-hydroxycitric acid. Both of these are untenable assertions. The difficulties with the first will be treated only after a consideration of the compound in question.

It must be borne in mind that sodium, potassium and calcium salts were already on the market at the time of the filing of this patent. Shrivastava, et al. themselves quite directly maintain that their material differs in effect from the (–)-hydroxycitrates already on the market. It is Shrivastava, et al. who write (column 2, lines 9-12),

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> a subject of the present invention is a new compound of (-)hydroxycitrate, namely magnesium (-)hydroxycitrate, in particular crystallized magnesium (-)hydroxycitrate, quite particularly substantially pure.

Moreover, those authors found it necessary even to distinguish their particular magnesium (–)-hydroxycitrate not only by form and purity as "in particular, crystallized magnesium (–)-hydroxycitrate, quite particularly substantially pure," but also by a process for preparation. *Magnesium (–)-hydroxycitrate, after all, was originally mentioned by Lowenstein in 1973 (US Patent 3,764,692).* In column 2, lines 13-23, Shrivastava, et al. indicate that

> A subject of the present invention is also a process for the preparation of magnesium (-)hydroxycitrate, characterized in that an extract of Garcinia cambogia is reacted with an aliphatic alcohol in order to obtain a precipitate which is subjected to the action of a tannin fixing agent, the solids are eliminated and the supernatant is recovered and subjected to batch chromatography on an anion exchanger resin, then left in contact under agitation, the supernatant is eliminated followed by elution of the magnesium (-)hydroxycitrate, the eluate is dried in order to obtain the expected magnesium (-)hydroxycitrate.

Hence Shrivastava, et al., in direct contradiction of the assertions made in the Office Action, maintain that there is an important distinction between magnesium (–)-hydroxycitrate, especially as produced by their method, and both (–)-hydroxycitric acid and other (–)-hydroxycitrates.

The Office Action maintains that "Shrivastava, et al. establish the interchangeability between (–)-hydroxycitrate and (–)-hydroxycitric acid." Where? No evidence from Shrivastava, et al. is provided for this assertion.

Despite the contrary assertion in the Office Action, in actual fact, Shrivastava, et al. take every opportunity to distinguish magnesium (–)-hydroxycitrate from both (–)-hydroxycitric acid and other (–)-hydroxycitrates. For instance, at the top of column 3, it is indicated that the composition must contain "at least magnesium (–)-hydroxycitrate as an active ingredient." Throughout the text, the references regarding efficacy are always to "magnesium (–)-hydroxycitrate" and never to (–)-hydroxycitric acid and other (–)-hydroxycitrates. Whether alone or in combination with either metals or vitamins, it is always "magnesium (–)-hydroxycitrate" and never to (–)-hydroxycitric acid and other (–)-hydroxycitrates.

Indeed, in the experimental section, when (–)-hydroxycitric acid is mentioned, *it is to indicate that this is not efficacious*, whereas magnesium (–)-hydroxycitrate is. Thus in Example 7 it is the "antioxidant effects of (-)hydroxycitrate and of different minerals" that are *contrasted* with those of magnesium (–)-hydroxycitrate. Again, under column 7, lines 14-23, we are told

> It can be observed firstly that the (-)hydroxycitrate alone has no protective effect on cell mortality. Magnesium alone reduces this mortality very slightly, whereas magnesium (-)hydroxycitrate has a more protective effect.

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> The magnesium (-)hydroxycitrate greatly reduces cell mortality (70.+-.8%), proving the protective effect of this product against oxidation damage.
>
> As regards the accumulation of lipids and cell proliferation, a very significant increase in the effects of magnesium (-)hydroxycitrate is observed with respect to (-)hydroxycitrate or magnesium.
>
> These results are quite unexpected.

In other words, despite the interpretation given in the Office Action, Shrivastava, et al. tell us that the effects of magnesium (–)-hydroxycitrate were not found by these inventors with (–)-hydroxycitric acid. Therefore, it can hardly be the case, as maintained in the Office Action, that "Shrivastava, et al. establish the interchangeability between (–)-hydroxycitrate and (–)-hydroxycitric acid." *Where do they do this?* The only evidence and argument given in the patent itself is to the contrary.

In short, despite the claim made in the Office Action, it is Shrivastava, et al. who argue that there is *no* interchangeability between magnesium (–)-hydroxycitrate and (–)-hydroxycitric acid. The remarks to the contrary in the Office Action ¶ 4, 12 and 13 fly in the face of both the examples and the language to the opposite effect given by Shrivastava, et al. themselves and therefore cannot be valid as an extension of this patent for objections to Clouatre, et al. on this point. How can it possibly be the case that the Office Action is going to teach the patent holders that they are wrong in their invention and then extend the reach of their patent in directions that they themselves expressly deny?

II Arguments from old chemistry text in Office Action wrongly extend remarks regarding carboxylic acids to tricarboxylic acids; errors both in logic and in fact, confusions in the Office Action as to whether it is the cation or the ligand that is active, etc.

The Office Action argues that one skilled in the art, especially after using the teachings of Shrivastava, et al., would look to substitute or replace one pharmaceutically acceptable cation for another, such as sodium or potassium or calcium? (See ¶ 4 and elsewhere.) Furthermore, the Office Action argues that there is a general interchangeability between (–)-hydroxycitrate and (–)-hydroxycitric acid. Aside from the now obvious fact that Shrivastava, et al. would not accept either argument, are these arguments logically or experimentally sound?

No, hardly. Let's start with the proposition that one can simply replace one cation with another. With regard to blood pressure, simply substitute "citrate" for "(–)-hydroxycitrate" and try the experiment with sodium. According to the logic of the Office Action, because magnesium citrate is known to lower blood pressure, then anyone skilled in the art would expect that substituting the cation sodium for magnesium will have the same effect. This, of course, will not happen. Sodium citrate raises blood pressure in those who are sodium sensitive and citric acid itself has no

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known effects on blood pressure at any physiologic dose. In the case of magnesium citrate, it is the cation that is active, not citric acid. The logic being used in the Office Action is false. Likewise, experimentally with other compounds the assertion found in the Office Action routinely turns out to be false. *The Office Action jumps back and forth between viewing either the cation or the ligand as being the active component, confusing these at will and providing no rationale at any point for its choice.* Contrarily, Shrivastava, et al., as noted above, maintain that magnesium (–)-hydroxycitrate *must always be present* in their invention.

Even with (–)-hydroxycitric acid, the assertion of "interchangeability" is demonstrably false in some cases. In US Patent 6,441,041 entitled, "(–)-Hydroxycitric Acid for the Prevention of Osteoporosis," we show that (–)-hydroxycitrate and (–)-hydroxycitric acid and increase body mineral density. However, we also specifically point out that, due to a different mechanism, over the long term large amounts of the free acid or its lactone may be less desirable because of the chelation of minerals. Clouatre, et al. have performed the experiments. Supposedly, Shrivastava, et al. also performed the experiments and denied expressly what the Office Action is trying to claim despite the clear language of the patent.

At various junctures, the Office Action maintains that Shrivastava, et al., demonstrate that there is a general interchangeability between (–)-hydroxycitrate and (–)-hydroxycitric acid. Where? This is to be found nowhere in the patent and the Office Action cites no actual lines. Instead, the Office Action puts words into the mouths of Shrivastava, et al. via ¶ 13 with references to various chemistry texts. However, it must be pointed out that (–)-hydroxycitrate is a tricarboxylic acid and not a simple carboxylic acid, such as citric acid. For many purposes, the chemistry is markedly different due to the fact that the inner valence point is often obscured by the external hydroxyl groups and also because odd and unpredictable kinetic factors come into play. Citing outdated chemistry texts not directed toward the chemistry of (–)-hydroxycitric acid is in many respects totally misleading and there is no good reason to expect otherwise.

The fundamental point remains that Shrivastava, et al. themselves deny the arguments being made in the Office Action. Those authors deny that their particular magnesium (–)-hydroxycitrate is comparable to other (–)-hydroxycitrates or interchangeable with (–)-hydroxycitric acid and they demonstrate that this is certainly not the case in at least one example. How does the Office Action justify ignoring the descriptions and examples found in the patent itself?

III Office Action remarks ¶14 based on DiPiro, et al. are partially contradicted even by the text being cited, improperly extend *inter alia* arguments and have no clear bearing on Clouatre, et al.

¶ 14, citing DiPiro, et al., does not appear to be clearly presented. Consequently, it is not clear as to how the inventors are supposed to respond. Not all hypertensive individuals are obese, even those who are diabetic. Many items used to treat obesity significantly raise blood pressure, e.g., ephedrine, Meridia (sibutramine), etc. Some items used to treat elevated blood sugar levels also lead to hypertension, as do some known anti-cortisol agents.

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Hence, although (–)-hydroxycitrates influence both insulin/blood glucose and blood pressure, there are compounds that do the former, but not the latter. *Gymnema sylvestre*, an Indian herb touted for to reduce blood sugar levels and treat diabetes, in animal experiments raised blood pressure. (Preuss HG, et al. Comparative effects of chromium, vanadium and gymnema sylvestre on sugar-induced blood pressure elevations in SHR. J Am Coll Nutr. 1998 Apr;17(2):116-23.)

Similarly, although (–)-hydroxycitrates influence both cortisol and blood pressure, there are compounds that do the former, but not the latter. RU-486 (Mifepristone), the French abortion pill and anti-glucocorticoid, unexpectedly raises blood pressure in some models. (Opoku J, Kalimi M. Role of the antiglucocorticoid RU 486 in the prevention of steroid-induced hypertension. Acta Endocrinol (Copenh). 1992 Sep;127(3):258-61.) It also suffers from various other issues, such as the induction of skin rashes.

The fact that (–)-hydroxycitrate influences obesity, insulin, cortisol, etc. as mechanisms is hardly a substitute for experimental evidence that the compound works as claimed. These are possible mechanisms, not endpoints, and are provided as such by Clouatre, et al. The pharmaceutical industry is littered with drugs that lowered this or that "marker," yet failed to positively affect endpoints. If one actually reads the DiPiro material sent in the Office Action, pages 809-810, one learns that "prolonged use of an oral hypoglycemic agent greatly increased cardiovascular mortality." This textbook was published in 1989 and, quite wrongly, asserts that this finding with regards to agents such as sulfonylurea turned out to not be true. Even a brief search shows that these oral agents seem to increase mortality rates even under the most recent of regimens for controlling their use. (Fisman EZ, et al. Oral antidiabetic treatment in patients with coronary disease: time-related increased mortality on combined glyburide/metformin therapy over a 7.7-year follow-up. Clin Cardiol. 2001 Feb;24(2):151-8.) Metformin is relatively safe in comparison, but it turns out that extreme caution still must be exercised.

Simply put, the very text cited in the Office Action fails to support the conclusions of the Action.

IV Proper characterization of Shrivastava, et al. to avoid conflicts with prior art and/or the conclusion that Shrivastava, et al. was issued in error

Choices regarding the compound found in Shrivastava, et al. must be revisited in the light of prior art. If the definition of the compound leads to internal contradictions and to confusions vis-a-vis other patents, then surely one must conclude that the wrong definition is being embraced. As noted above, the possible alternatives are these:

a) magnesium (–)-hydroxycitrate is an entirely new substance
b) magnesium (–)-hydroxycitrate is a special salt of magnesium *unique due to its ligand (–)-hydroxycitric acid*, which gives this form of magnesium special properties
c) magnesium (–)-hydroxycitrate is a form of (–)-hydroxycitric acid identified by the choice of the alkaline earth metal magnesium used to produce the salt with properties shared by all other forms of the acid and its salts

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d) magnesium (–)-hydroxycitrate is a new compound of (–)-hydroxycitrate with properties that are unique to itself and not shared with (–)-hydroxycitric acid nor other salts of (–)-hydroxycitric acid

The Office Action cannot avoid making a determination among the above. Such a determination will, in turn, prove decisive in the evaluation of the novelty of the claims of Clouatre, et al.

There is little need to examine in depth choice (a) because it makes no sense inasmuch as the compound is not sufficiently characterized. True, a process is provided for its production, but there is no X-ray crystallography or other test provided to distinguish this salt from the same salt produced by any of myriads of alternate methods. Also, magnesium (–)-hydroxycitrate is not presented by Shrivastava, et al. as a new substance *per se*, but rather they (evidently by not citing the prior art of Lowenstein) expressly claim it to be a new compound.

It has been shown already that choice (c), the choice simply assumed in this and previous Office Actions, cannot be defended. First, it is expressly denied by Shrivastava, et al. in the text of the patent. Second, it is refuted by one or more of the examples given by Shrivastava, et al. Furthermore, as will be shown here, (c) shares with (d) the additional disadvantage of introducing confusion with regard to other patent claims and published prior art.

This brings up an unavoidable issue. In ¶ 4 Office Action states in regards our discussions of Lowenstein and other prior art that "this reference was not used in a rejection so it will not be discussed...." Undoubtedly this is in error as it leads directly to an interpretation of Shrivastava, et al. which is at odds with at least two earlier patents as well as massive amounts of other prior art. Surely prior art expressly addressing the same matter as a patent claim is always relevant? To hold otherwise is to refute the requirement that all administrative standards must be consistent and equitable, that they should not give grounds for contradictions between past and present claims or actions, nor should they set the stage for an increased burden upon the courts in the interpretation of the extent of patent rights.

Choices (c), the interpretations adopted by the current Office Action, and (d) lead directly to contradiction and confusion with past art. Shrivastava, et al. make the following claims:

> 9. In a method for the preparation of a medicament for the treatment of a cardiovascular disease and comprising a cardiovascular-effective compound in a quantity sufficient to provide a cardiovascular effect, the improvement wherein magnesium (-)hydroxycitrate is used as said cardiovascular-effective compound or as at least one said cardiovascular-effective compound.
>
> 10. In a method of treating a cardiovascular disease in a patient in need thereof with a cardiovascular-effective compound, the improvement comprising using magnesium (-)hydroxycitrate in a cardiovascular-effective amount in said method.

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19. In a method for treating athermatony disease in a patient in need thereof, the improvement comprising using magnesium (-)hydroxycitrate in an effective amount to treat accumulation of lipids in cells of vascular smooth muscles.

20. A method for treating hypercholesterolemia comprising administering to a patient in need thereof an effective amount of magnesium (-)hydroxycitrate.

According to the interpretation given in the Office Action, ¶ 4 at the top of page 3 and referring to the previous Office Action of 25 November 2002, it is stated that one skilled in the art, especially after using the teachings of Shrivastava, et al., would look to substitute or replace one pharmaceutically acceptable cation for another, such as sodium or potassium or calcium. Later, the present Office Action further maintains that Shrivastava, et al. establish the interchangeability between (–)-hydroxycitrate and (–)-hydroxycitric acid. The quite obvious implication is that (–)-hydroxycitric acid prior to Shrivastava, et al. had never been suggested as having efficacy in the treatment of cardiovascular disease nor had it been suggested as influencing cholesterol and other blood lipids, etc.

This startling conclusion by the Office Action is demonstrably not true. Claims regarding hypolipemia and the reduction in the synthesis of cholesterol (e.g., Claim 20) were already to be found abundantly in the literature with regard to (–)-hydroxycitrate prior to Shrivastava, et al. *Consequently, if Shrivastava, et al. do not in fact present (–)-hydroxycitrate as merely a ligand for magnesium, then various claims in the issued patent fail instantly in the face of prior art stretching back almost thirty years.* One set of authors — and I stress this is only one of many sources — published the following in 1972:

> Fatty acid and cholesterol synthesis were inhibited in a similar manner by different (–)-hydroxycitrate concentrations. As *in vivo*, this compound appears to only partially inhibit fatty acid synthesis in the perfused organ.
>
> The similarity of the (–)-hydroxycitrate effect on cholesterol and fatty acid synthesis is suggestive of a common mechanism of inhibition, e.g. lowering of the cytoplasmic acetyl-CoA level. This assumption requires that both effects be abolished by replenishment of the acetyl-CoA pool by exogenous acetate. While this was verified for fatty acid synthesis, ^{3}H-incorporation into cholesterol was not normalized by acetate addition."
>
> Barth, C., J. Hackenschmidt, H. Ullmann, and K. Decker (1972). Inhibition of cholesterol synthesis by (–)-hydroxycitrate in perfused rat liver. Evidence for an extramitochondrial mevalonate synthesis from acetyl coenzyme A.
> **FEBS Letters** 22, 3 (May 1972) 343-346.

Similarly, Claim 19 regarding a reduction in the accumulation of lipids in vascular smooth muscles would appear to be a direct extension of work previously performed which showed that (–)-hydroxycitrate increases the catabolism of LDL cholesterol. The clear implication of this action under consensus medical thinking at the time of the filing of Shrivastava, et al. is that the

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collection of lipids in the artery wall would be reduced. Very curiously, no prior art of this nature is disclosed by Shrivastava, et al. and there is no discussion of these properties of (–)-hydroxycitrate in Shrivastava, et al.

> The most significant finding in the present work is that overnight exposure of Hep G2 cells to the ATP citrate-lyase inhibitor (–)-hydroxicitrate results in an up-regulation of LDL receptor activity and LDL-receptor-dependent LDL catabolism.
>
> Berkhout, Theo A., Louis M. Havekes, Nigel J. Pearce and Pieter H. E. Groot (1990). The effect of (–)-hydroxycitrate on the activity of the low-density-lipoprotein receptor and 3-hydroxy-3-methylglutaryl-CoA reductase levels in the human hepatoma cell line Hep G2. **Biochemistry Journal** 272, 1 (1990) 181-186.

It is the interpretation of the Office Action that creates the above contradictions and confusion. Similarly, if the interpretation of the Office Action is accepted, then Lowenstein (1973 US Patent 3,764,692) is brought directly into conflict with Shrivastava, et al. Lowenstein refers specifically to magnesium (–)-hydroxycitrate. Whether one refers to it as a "new substance" or as a "new compound," incontrovertibly there is prior art in the form of issued patents dating from as far back as 1973 regarding magnesium (–)-hydroxycitrate. This fact is difficult – logically perhaps impossible – to harmonize with Shrivastava, et al., who write (column 2, lines 9-12),

> a subject of the present invention is a new compound of (-)hydroxycitrate, namely magnesium (-)hydroxycitrate, in particular crystallized magnesium (-)hydroxycitrate, quite particularly substantially pure.

Not just Lowenstein, but other patent holders as well would find the interpretation set forth in the Office Action to be untenable. For instance, we find in United States Patent 6,217,898 issued to Cavazza on 17 April 2001 the following:

> Hydroxycitric acid, too, has for some time now been known as a metabolic factor. It is present, in fact, in large amounts in a number of plants used as foodstuffs and, in particular, in Malabar Tamarind and in the fruits of various species of Garcinia and its extraction and isolation have permitted extensive biochemical and pharmacological study of the substance. Recent data have revealed its importance as a regulator of the synthesis of cholesterol and fatty acids (Hamilton Y. G., Lipids 12, 1, 1976).
>
> Hydroxycitric acid is capable of inhibiting the activity of ATP-citratolyase, an enzyme which catalyses the extramitochondrial conversion of citrates to oxoacetates and acetyl Coenzyme A.

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> The importance of this enzyme consists in its ability to maintain the Coenzyme A pool necessary for lipid and cholesterol synthesis. The enzymatic reaction catalysed by citratolyase which leads to the synthesis of cholesterol and fatty acids from carbohydrates is inhibited by hydroxycitric acid which together with the reduction in lipid synthesis also leads to a greater storage of carbohydrates in the form of glycogen in the liver (Berkbout T. A., Biochem. J. 48, 6, 1990; Triscari Y., Sullivan A. C., Lipids 12, 357, 1976; Watson Y. A., Fang M., Arch. Biochem. Biophys. 135, 209, 1969).
>
> Both L-carnitine and hydroxycitric acid are, therefore, capable of exerting an action upon lipid metabolism via different mechanisms: on the one hand, L-carnitine facilitates the oxidation and intramitochondrial utilization of fatty acids and prevents the accumulation of triglycerides, and, on the other, hydroxycitric acid prevents their actual synthesis (Lowenstein Y. M., J. Biol. Chem. 246, 629, 1971; Hood R. L., Comp. Biochemical Physiol. 81B, 667, 1985).

In other words, Shrivastava, et al. had no choice but to make the preposterous claim that theirs is a new compound and not (–)-hydroxycitrate in general nor a property of (–)-hydroxycitric acid because their claims had been roundly anticipated if those interpretations were applied. Moreover, what seems to be obvious is that Shrivastava, et al. relied on the distinction between magnesium hydroxycitrate and all other (–)-hydroxycitric acid salts to get their patent in the first place. Of the four choices for interpretation that are available, only (b) can be harmonized with the prior art and offer any option other than that the patent was issued in error. *Hence, it must be that Shrivastava, et al. claim no more than to have discovered that magnesium (–)-hydroxycitrate is a special salt of magnesium unique due to its ligand, (–)-hydroxycitric acid, which gives this form of magnesium special properties. The salt itself most definitely is not their invention. They do not – indeed, cannot – extend their claims beyond this point.*

V Claims made for magnesium with (–)-hydroxycitric acid as a ligand (Shrivastava, et al.) versus claims made for (–)-hydroxycitric acid with or without magnesium as a cation (Clouatre, et al.)

Shrivastava, et al.'s teaching regarding magnesium (–)-hydroxycitrate is analogous to claiming that vitamin E succinate has special properties as opposed to either vitamin E or succinic acid. In the case of vitamin E, a claim for vitamin E succinate does not mean that either vitamin E alone or vitamin E with other ligands (such as acetate) will have the same properties as vitamin E succinate — which, by the way, acetate does not. In the Shrivastava, et al. patent, it is the magnesium, the cation, that is the active component, but its potentiation is via the ligand. Shrivastava, et al. themselves demonstrate this in their Example 7.

Shrivastava, et al. relied on the distinction between magnesium (–)-hydroxycitrate and all other (–)-hydroxycitric acid salts to get their patent in the first place. The simple fact of the matter is that Shrivastava, et al. did not know, let alone teach, that a hypotensive effect is characteristic of hydroxycitric acid. What Shrivastava, et al. do teach is that magnesium is somehow potentiated

by using hydroxycitric acid as a ligand. This is all that they teach, and such is reasonably clear simply from reading what they wrote in the patent.

If Shrivastava, et al. is interpreted as making claims for magnesium which is potentiated through the use of (–)-hydroxycitric acid as its ligand, it is possible to achieve harmony with the manner in which the patent describes matters in its text, examples and claims. It is also possible to avoid most outright contradictions and confusions involving patents and other prior art. Using the present interpretations found in the Office Action, to the contrary, leads to contradictions within Shrivastava, et al., to the necessity of discounting both the words and the examples of Shrivastava, et al., and to the creation of confusion with regard to at least two already issued patents. The only other choice is to find that Shrivastava, et al. was issued in error.

The consequence of this proposed reading is that *Shrivastava, et al. must be interpreted as making a hypotensive claim only for a magnesium salt, in particular magnesium which has been potentiated with (–)-hydroxycitric acid as the ligand*. This means that Shrivastava, et al. have not taught regarding either (–)-hydroxycitric acid or its salts as such, nor have they taught regarding magnesium *per se*. This interpretation is entirely in line with the distinctions drawn in the experiments.

It is Clouatre, et al., who discovered that (–)-hydroxycitric acid reduces elevated blood pressure, possibly via glucocorticoid, insulin, leptin or other mechanisms, and that this quality is passed on to the salts with varying levels of efficacy dependent in part upon uptake. The teachings of Clouatre, et al. revolve around (–)-hydroxycitric acid, its salts, amides and esters and are not dependent upon any particular cation.

Conclusion

The interpretation offered in this and previous Office Actions is systematically at odds with the wording and examples found in Shrivastava, et al. and leads directly to infringements on prior art. It therefore cannot possibly be an acceptable interpretation unless one deems the patent by Shrivastava, et al. itself to have been issued in error.

Attempts to extend the reach of Shrivastava, et al. via notions of substitutions or replacements of one pharmaceutically acceptable cation for another have been shown to be misguided. Similarly, it has been demonstrated that the proposed interchangeability between (–)-hydroxycitrate and (–)-hydroxycitric acid voiced by the Office Action cannot be supported from the text and examples of that patent, indeed fly in the face of the clear wording of the patent itself. Moreover, neither of these approaches can withstand logical or empirical scrutiny.

Hence, Clouatre, et al. offer a different determination of the substance to which the claims of Shrivastava, et al. can be applied without introducing confusions vis-a-vis previous patent claims and other prior art.

Yours truly,

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To: **Examiner Dwayne C. Jones (USPTO)**

From: Dallas Clouatre

Re: Response to Office Action

Message:

Assistant Commissioner for Patents
U.S. Dept. of Commerce / Patent & Trademark Office
Attn: Examiner Dwayne C. Jones, AU 1614
Washington, D.C. 20231

RE: Pat. Application #09/781,491
Clouatre, et al., Methods And Pharmaceutical Preparations For Normalizing Blood Pressure With (–)-Hydroxycitric Acid
Office Action of 06/06/2003 in response Inventor's document mailed 01/20/03